REMARKS

Claims 1, 5-11, and 13-16 are pending in the instant application. Claim 16 stands objected to under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claims 1, 5-11, and 13-16 stand rejected under 35 U.S.C. §103(a) as being unpatentable over United States Patent No. 6,574,495 to Golman et al. or United States Patent No. 6,278,893 to Ardenkjaer-Larson et al. in view of either United States Patent No. 5,245,282 to Mugler et al. or United States Patent No. 6,310,478 to Held. The application has been amended. Claim 16 has been amended to correct an antecedent basis problem. Applicants respectfully submit that none of the amendments constitute new matter in contravention of 35 U.S.C. §132. Reconsideration is respectfully requested.

Claim 16 stands objected to under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. More specifically, claim 16 is cited for insufficient antecedent basis for the term "the vascular bed". Applicants respectfully submit that this rejection stand obviated in view of the amendment to claim 16 whereby the definite article 'the' preceeding "vascular bed" has been replaced by the indefinite article 'a'. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1, 5-11, and 13-16 stand rejected under 35 U.S.C. §103(a) as being unpatentable over United States Patent No. 6,574,495 to Golman et al. or United States

Patent No. 6,278,893 to Ardenkjaer-Larson et al. in view of either United States Patent No. 5,245,282 to Mugler et al. or United States Patent No. 6,310,478 to Held. This rejection is respectfully traversed.

As the Examiner correctly points out, Golman et al. or Ardenkjaer-Larsen et al. disclose methods of MR imaging using hyperpolarised MR agents in liquid phase. Golman et al. or Ardenkjaer-Larsen et al. fail to disclose the features of the method of the invention or using both a FISP or PSIF pulse sequence with a flip angle of 45 to 90 degrees.

The technical problem solved by using a FISP or PSIF pulse sequence with a flip angle of 45 to 90 degrees for a hyperpolarised imaging agent in liquid phase is to avoid a reduced signal due to increased T_2 relaxation rate of the imaging agent. Such an increased T_2 relaxation is caused by physiological changes (e.g. pH or temperature) or short half life of the imaging agent due to metabolism (see page 14, 3rd paragraph of the present application) – the latter being most important since the imaging agent of the present invention is a compound of interest in metabolic studies, i.e. a compound that is metabolised.

Ardenkjaer-Larsen et al. teaches away from using a FISP or PSIF pulse sequence for hyperpolarised MR imaging agents in liquid phase since there are more advantageous pulse sequences for liquids known like EPI (see Col. 5, lines 21-23). Clearly the skilled person in the art faced with the aforementioned technical problem would not have considered using a less efficient pulse sequence when being presented with more efficient and advantageous alternatives.

Mugler et al. and Heid disclose a FISP pulse sequence which is used in MR imaging methods. However, neither reference discloses, teaches, or suggests liquid hyperpolarised MR imaging agents. In fact, Heid does not disclose the use of any MR imaging agents at all while the only imaging agent disclosed by Mugler et al, Gd-DTPA (col. 19, lines 21-24), is a thermally polarised liquid MR imaging agent. The main difference between a thermally polarised liquid MR imaging agent like Gd-DTPA and a liquid hyperpolarised MR imaging agent is that in the former's changes in contrast are caused by affecting the relaxation times of water protons in a patient's body whereas the latter can be regarded as non-radioactive tracers, as the MR signal obtained arises solely from the hyperpolarised MR imaging agent itself.

For steady-state imaging (FISP and PSIF are pulse sequences for steady-state imaging) of thermally polarised liquids, a radio-frequency pulse is emitted in a preparation phase preceding the pulse sequence (see Heid, col. 1, lines 27-29) which is required to realise such a steady state. In thermally polarised liquids, T1 relaxation has the positive effect of renewing longitudinal magnetisation during the execution of the pulses. In hyperpolarised liquids however, such pre-scans have the negative effect of destroying the non-renewable magnetisation such that a steady state is only established when the magnetisation has been reduced to the thermal equilibrium. This would, however, mean that all the advantages derived from the hyperpolarisation (page 3, 1st paragraph of the application) are no longer available. Hence the present invention teaches, for hyperpolarised liquids, the taking of a "pseudo-steady-state" approach (see page 13, last paragraph of the application).

For obtaining high signal intensity with conventional thermally polarised liquids, the flip angle can be optimized and optimal signal intensity may be obtained. For hyperpolarised liquids, one not only has to realize that the equation T1 = T2 (for flip angle optimization) is not applicable, but also that due to T1 relaxation the magnetisation constantly decreases. This leads to a more complicated theoretical approach where such a simple flip angle optimization is no longer possible. Moreover, in the case the hyperpolarised liquid being a compound that is metabolized, the compound "disappears" due to the metabolisation and hence the equation T1 = T2 is no longer applicable at all.

Therefore, the prior art discussion about FISP and steady state imaging is exclusively related to thermally polarised liquid compounds. Moreover, the relationships that are true for thermally polarised liquid compounds are not applicable for hyperpolarised liquid compounds. In view of this Applicants respectfully submit that the use of a pulse sequence 1) from which Ardenkjaer Larsen et al. teaches away and 2) which has only been used and optimized for thermally polarised liquid MR imaging agents would not be obvious to combine with the flip angles for hyperpolarised liquid compounds. Instead the instant invention realizes that by using such a FISP or PSIF sequence with a flip angle of 45 to 90 degrees, on a hyperpolarised imaging agent in liquid phase, a reduced signal (due to increased T_2 relaxation rate of the imaging agent) could be avoided. Thus, Applicants respectfully submit that one of ordinary skill in the art would not seek to combine the cited references as suggested by the Examiner. In view of the teachings of the prior art failing to disclose, teach, or suggest the instant invention, Applicants respectfully submit that the instant invention is patentably distinct over the cited references. Reconsideration and

withdrawal of the rejection are respectfully requested.

In view of the amendments and remarks hereinabove, Applicants respectfully submit that the instant application, including claims 1, 5-11, and 13-16, is in condition for allowance. Favorable action thereon is respectfully requested.

Any questions with respect to the foregoing may be directed to Applicant's undersigned counsel at the telephone number below.

Respectfully submitted,

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